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A 4-year old presenting with fever and achiness

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Abstract

In children under the age of 5 who have abnormalities in history, physical examination, and laboratory studies indicating multi-system disease, uncovering the correct diagnosis is challenging. Here, we report the course of a 4-year-old girl who presented with a change in behavior, fever, arthralgia, arthritis, and hematuria following three recent hospitalizations for pneumonia and impetigo. Serologic findings were suggestive of a rheumatologic etiology and a renal biopsy was consistent with Membranous Lupus Nephritis Class V which helped secure the diagnosis of pediatric systemic lupus erythematosus. We review the clinical features and diagnostic criteria of early-onset systemic lupus erythematosus and discuss diagnostic considerations and prognosis.

Keywords

Rheumatology/clinical immunology, pathology, nephrology

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Introduction

Systemic lupus erythematosus (SLE) is a chronic inflammatory autoimmune disease commonly involving multiple organ systems. It is challenging to diagnose because of its highly variable presentation. Pediatric systemic lupus erythematosus (pSLE), also called childhood-onset SLE, describes disease fulfilling diagnostic criteria for SLE in children younger than the age of 18.[1] pSLE comprises 10%–20% of SLE diagnoses; however, it is uncommon in children under the age of 5. Recognizing pSLE is additionally challenging because pSLE criteria have not been established. This uncertainty can decrease clinical suspicion and delay diagnosis when young pediatric patients develop SLE. Rarely, pSLE presents in children younger than 5 years old; these cases can be difficult to recognize and are associated with greater risk for organ system damage and mortality.[2–4]

Early identification and prompt treatment, while difficult, is of particular importance in this age group. Here, we present the case a 4-year-old girl who was evaluated for a broad diagnostic differential, eventually leading to the diagnosis of pSLE.

Case report

A 4-year-old girl with a history of eczema and absence seizures treated with ethosuximide presented with persistent fever, migratory joint pain, joint swelling, and hematuria. She was last at her baseline state of health 3 months prior to presentation, after which she experienced recurrent fevers and was hospitalized three times for pneumonia and impetigo. She then developed arthralgia, joint swelling, abdominal pain, fever, sore throat, cough, and change in behavior, prompting admission to a referring hospital. She was diagnosed with acute otitis media, started on ciprofloxacin, and transferred to our hospital for further management.

At admission, her temperature was 37.5°C, heart rate was 115 beats/min, respiratory rate was 20 breaths/min, and blood pressure was 121/84 mmHg. She appeared uncomfortable and was "not herself" according to her mother. Physical examination revealed diffuse polyarthritis and tender generalized lymphadenopathy. There were no appreciable skin rashes, mucosal changes, cardiac murmurs, or pleurodynia. She did not have any history of travel outside the United States, toxic exposures, or contact with

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other sick children. Family history was significant for SLE in her paternal grandmother's sister. There was no family history of consanguinity.

Admission laboratory studies were significant for anemia (hemoglobin 10.5 g/dL, range: 11.5–14.5 g/dL), elevated erythrocyte sedimentation rate (ESR; >145 mm/h, range: 0–20 mm/h), elevated C-reactive protein (1.12 mg/dL, range: 0.0–0.9 mg/dL), and a positive Direct Coombs test. White blood cell count ($9.1 \times 10^3/\mu L$, range: $4.0–12 \times 10^3/\mu L$), platelets ($267 \times 10^3/\mu L$, range: $150–450 \times 10^3/\mu L$), and thyroid-stimulating hormone (1.34 UIU/mL, range: 0.66–4.75 UIU/mL) were within normal limits. HIV and tuberculosis testing were negative. Urinalysis was notable for 30 mg/dL of protein as well as 15 red blood cells per high-power field. Quantitative urine protein-to-creatinine ratio was 1790 mg/g (nephrotic range > 3500 mg/g).[5] The calcium-to-creatinine ratio was 0.07 (normal range <0.2).[6] There was no microbial growth on urine cultures. Creatine kinase was within normal limits. Serum complement studies were notable for low C3 (48 mg/dL, range: 86–166) and low C4 (6 mg/dL, range: 9.7–36). C1q immune complex binding protein was high (61 mcg Eq/mL, range ⩽ 25). She was also positive for both lupus anticoagulant and anticardiolipin antibodies. Recent outpatient rheumatology labs revealed an ESR of 77 mm/h, elevated antinuclear antibodies (ANA; >1:1280), as well as positive anti-double-stranded DNA (dsDNA), anti-Smith and anti-ribonucleoprotein antibodies. Unfortunately, her symptoms worsened before she could follow up on these results in clinic.

Brain magnetic resonance imaging (MRI) with arterial and venous phase contrast was done due to abnormal behavior; no intracranial pathology or vascular abnormalities were present. Abdominal ultrasound revealed grade 2 pelviectasis in both kidneys, mild distension of the right renal pelvis, slight hepatomegaly, increased mesenteric echogenicity, trace pelvic free fluid, and no masses.[7] A bone marrow biopsy—performed due to her arthralgias and lymphadenopathy—showed mildly hypocellular bone marrow with no blasts or other pathology. To further investigate the hematuria and proteinuria, a kidney biopsy was done, which revealed mild mesangial hypercellularity and immune complex membranous glomerulonephritis with full house IgM/C3-dominant staining on immunofluorescence and reticular aggregates on electron microscopy, consistent with Membranous Lupus Nephritis Class V (Figure 1).[8]

Final diagnosis

Final diagnosis is done by pSLE.

Hospital course

During her hospitalization, acetaminophen and ibuprofen were given for pain and fever control, and amlodipine for blood pressures above the 95th percentile for age. Ethosuximide was temporarily held and then restarted for seizure prophylaxis. Upon diagnosis of pSLE, she was treated with high-dose pulse intravenous methylprednisolone for 3 days, followed by oral maintenance prednisolone. By discharge, she was afebrile with significant decrease in her pain. She was discharged on hydroxychloroquine for immunomodulation. In a follow-up visit with outpatient rheumatology, a primary immunodeficiency panel (Invitae) was sent, however was unrevealing.

Discussion

This girl's age of SLE onset is particularly notable; while there are several case reports of children presenting with SLE under age 5, it remains quite uncommon.[4,9] Furthermore, she lacked any mucocutaneous involvement, which is present in approximately 70% of patients with pSLE at presentation.[2,10] Nonetheless, this girl had many classic features of SLE, including Coombs positive anemia, representing hematologic involvement, seen in about 72% of pSLE patients at presentation.[2,10] She also demonstrated musculoskeletal involvement in the form of polyarthritis and myalgias, which appears in 64% of pSLE patients.[2,10] Renal involvement was evident with hematuria and proteinuria. This girl showed immunological involvement, testing positive for both anti-dsDNA and anti-Smith lupus-specific antibodies. She had low complement levels, and elevated C1q immune complex binding protein, suggesting a consumptive process and immune complex formation. While she had normal immunoglobulin levels, it is not uncommon to see hypergammaglobulinemia in patients with SLE. Notably, based on some diagnostic criteria for pSLE, this girl's renal biopsy findings were independently sufficient to diagnose SLE.

Currently, pSLE is diagnosed using modified versions of adult criteria including the American College of Rheumatology (ACR) criteria, Systemic Lupus International Collaborating Clinics (SLICC) classification criteria, and European League Against Rheumatism (EULAR).[11–13] However, the current diagnostic criteria for pSLE are limited, as no widely accepted criteria have been developed specifically for this age group. We used the SLICC criteria, which has been shown to have a higher sensitivity diagnosing SLE in children, although it has lower specificity.[12] SLICC criteria requires either that a patient demonstrates lupus nephritis on renal biopsy with the presence of ANA or anti-dsDNA antibodies, or manifests at least four of the criteria findings, with at least one from each of the immunological and clinical categories.[14] Clinical findings include cutaneous, joint, renal, and hematologic involvement.[14] Immunological markers include anti-dsDNA (84% sensitivity in pSLE) and anti-Smith antigen (48% sensitivity in pSLE), which are more specific for SLE.[12,13]

Despite sharing diagnostic criteria, pSLE and adult SLE (aSLE) often present differently. Specifically, pSLE patients have higher rates of lupus nephritis, seizures, cerebrovascular events, and hemolytic anemia compared to aSLE.[15,16] Appropriately, in pSLE patients, clinicians should be vigilant of renal and neurological disease and should carefully

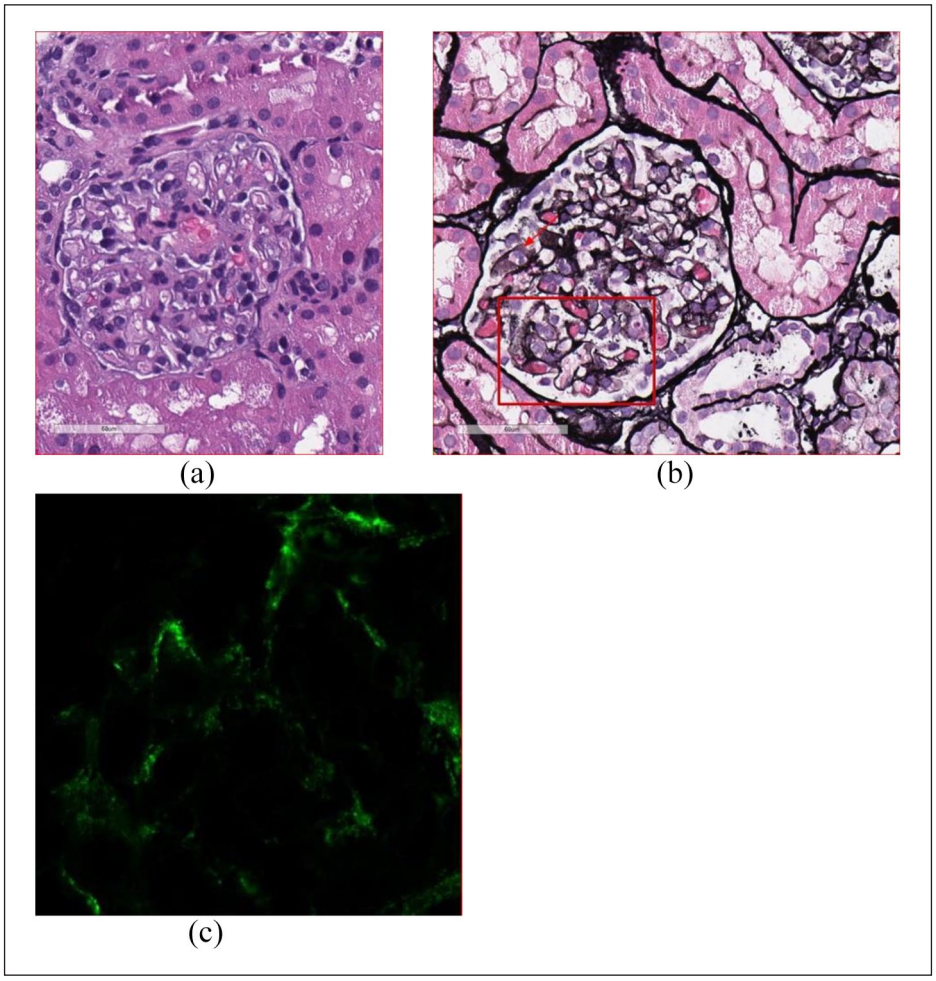

Figure 1. Renal biopsy microscopic images. (a) Hematoxylin and eosin (H&E) stain at 40× magnification showing a glomerulus showing mild mesangial increase in cells. (b) Jones/Periodic Acid-Schiff (PAS) stain at 40× showing glomerulus with focal glomerular capillary wall thickening (rectangle) and vacuoles (arrow). (c) IgM immunofluorescence showing deposits in capillary walls.

review the urinalysis and serum creatinine while surveying for edema, altered mental status, and focal neurologic deficits on physical examination. Findings suggestive of lupus nephritis, such as significant proteinuria or hematuria, should prompt consideration of renal biopsy. This is critical as pSLE patients with lupus nephritis can progress to end-stage renal disease (ESRD), which is associated with a 5-year mortality of 22% following renal replacement therapy.[17,18] By maintaining high suspicion for pSLE, even in children younger than age 5 with no mucocutaneous features, these poor outcomes can potentially be avoided.

When a child presents with fever, migratory joint pain, and hematuria, it is critical to start with a broad differential including infection, malignancy, and underlying immunological deficiency which can mimic pSLE. This is particularly vital for patients under age 5 for whom pSLE is uncommon. Although not exhaustive, the differential includes infection (cytomegalovirus (CMV), Epstein–Barr virus (EBV), and post-streptococcus sequelae), rheumatological etiologies (systemic vasculitis, juvenile idiopathic arthritis, SLE, and drug-induced SLE), and oncologic etiologies (leukemia or lymphoma). Workup includes laboratory studies (complete metabolic panel, complete blood count, serum markers of inflammation, and urinalysis) and physical assessment (including neurological, musculoskeletal, and dermatologic examinations, with attention to mucous membranes and lymph nodes). Infectious workup for the girl in this case study was negative, bone marrow biopsy with no blasts or hypercellularity made leukemia unlikely, and the presence of anti-dsDNA, hypocomplementemia, anemia, and renal biopsy consistent with SLE led to the diagnosis of pSLE.[19] Ethosuximide is associated with drug-induced SLE; however, this is usually associated with a negative dsDNA and normal complement levels, making this etiology less likely. Of note, anti-histone antibodies are often present in patients with drug-induced lupus (>95% positive); however, they may also be present in primary SLE (70% positive).[20]

The genetic underpinnings of SLE are an active area of research. Polymorphisms associated with increased risk of

SLE include complement deficiencies (C1q, C2, and C4), specific human leukocyte antigen genotypes (HLA-B8, HLA-DR2, HLA-DR3), and genes coding for interferon regulatory factor 5 and protein tyrosine phosphatase N22.[21] If early-onset SLE or recurrent infections are present, the patient should be assessed for immunodeficiency. Low or absent classical complement pathway components (C1-4) can be a result of consumption by immune complexes (as seen in active SLE) or genetic deficiency, respectively. Such complement deficiencies, as well as other primary immune deficiencies, may predispose to SLE.[22]

Conclusion

In summary, children younger than 5 years old who have abnormalities in their history, physical examination, and laboratory studies indicating multi-system disease should be evaluated for pSLE and other similarly presenting diseases. For this young girl, infection, malignancy, and other diagnoses of consequence were ruled out and then pSLE was diagnosed. The diagnosis was established with the SLICC criteria, kidney biopsy results, positive ANA, presence of lupus-specific autoantibodies, polyarthritis, Coombs positive anemia, and low serum complement levels.

The lack of prototypical malar rash and other mucocutaneous findings in this girl underscores the variable presentation of pSLE, especially in very young children. By maintaining a high index of suspicion for pSLE in this population, clinicians can select appropriate clinical and laboratory testing, establish a diagnosis, and provide timely treatment. Early intervention is key to mitigating the morbidity and mortality associated with pSLE.

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